D/cont

at least a portion of said oligodeoxyribonucleotide being in a stabilized form in order to limit degradation in vivo;

introducing said oligodeoxyribonucleotide into a cell; and

hybridizing said oligodeoxyribonucleotide with said base sequence of said messenger ribonucleic acid coding for said targeted protein, whereby translation of said base sequence is substantially blocked and synthesis of said targeted protein is inhibited.

REMARKS

In the August 6, 1991 Office Action, the Examiner had rejected claim 62 under 35 U.S.C. § 101 on the grounds of double-patenting. The Examiner remarked that claim 62, which claims a method of inhibiting in vivo synthesis, covered the same subject matter as that of claim 1 of prior U.S. patent No. 5,023,243. This latter claim was limited to the phosphotriester derivatives of oligonucleotides. In response to the rejection, the Applicant cancelled claim 62, which contained the same limitation. Applicant now submits new claim 63 which is not limited to the phosphotriester derivatives. Applicant respectively submits that this new claim satisfies the requirements of 35 U.S.C. § 101 and should, therefore, be allowed.

Section 112, 1st paragraph

Claims 53-61 stand rejected under 35 U.S.C. § 112, first paragraph, a new grounds of rejection. The Examiner contends that the disclosure is enabling only for claims utilizing phosphotriester derivatives of oligodeoxyribonucleotides. The Examiner argues that without guidance in connection with other forms of stable oligonucleotides, it would require undue experimentation for one of skill in the art to discover and synthesize the compounds.

The Applicant respectively disagrees. The application need not disclose each and every method of preparing stabilized forms of oligonucleotides where such methods were well within the knowledge of those skilled in the art at the time the application was filed. Hybritech v. Monoclonal Antibodies, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986)(a patent need not teach and preferably omits what is well known in the art).

To support his argument, the Applicant cites below several references, attached hereto as Exhibits A through E, which disclose the preparation and/or use of stabilized forms of oligonucleotides. Although the publication dates of several of the references are subsequent to the application's filing date, their submittal is appropriate since the references are offered not to supplement an insufficient disclosure but rather as evidence of the level of skill in the art at the time of filing. Gould v. Quigg, 3 U.S.P.Q.2d 1302, 1305 (Fed. Cir. 1987).

Ts'o et al. (U.S. patent 4,469,863) discussed the unique physical and biological properties of non-ionic analogues of nucleic acids such as oligonucleoside alkyl- and aryl phosphonates. They specifically disclosed methods of preparing oligonucleoside methylphosphonates, a stabilized form possessing the property, among others, of being resistant to hydrolysis by nucleases. Miller et al., Nucleic Acids: *The Vectors of Life*, 521-535 (1983) - (Exhibit A).

The stability of oligonucleotides has also been enhanced through the use of phosphorothioate linkages. Vosberg et al. (*J.Biol.Chem.* 257(11) 6595-6599 (1982)) - (Exhibit B), investigated the effect of phosphorothioate groups in DNA on the cleavage pattern of restriction endonucleases. Their results showed that, in general, the presence of such groups at the site of cleavage decreased the rate of hydrolysis. In Connolly et al. (*Biochem.* 23(15) 3443-53 (1984)) - (Exhibit C), an octanucleotide

containing a phosphorothioate internucleotide linkage at the endonuclease cleavage site exhibited a hydrolysis rate slower than that of the unmodified oligonucleotide. Moreover, Harvey et al. (*Biochem.* 12(2) 208-214 (1973)) - (Exhibit D) utilized alkylthio groups to serve as 5'-terminal protecting groups during the synthesis of oligonucleotides. Although used as terminal blocking groups, these groups were retained throughout the synthesis process. Thus, one skilled in the art would have been aware that the stabilizing effect of alkylthio groups was not limited to end groups but rather could be extended throughout the oligonucleotide chain. In addition, Malkievicz et al. (*Czech.Chem.Commun.* 38, 2953-2961 (1973)) - (Exhibit E) discussed the use of alkyl thioyl groups as blocking groups in the stepwise synthesis of oligonucleotides. The authors noted that while these analogs maintained the ability to form double-stranded polymers and the messenger ability, they were more resistant towards nucleases than the parent substances. In summary, the analogs represented a stabilized form of the parent oligonucleotides.

These publications evidence that methods of preparing stabilized forms of oligonucleotides were known in the art at the time the application was filed. As long as a specification is enabling to a person skilled in the art, it satisfies the enablement requirement of 35 U.S.C. § 112. Therefore, the rejection should be withdrawn.

Section 112, 2nd paragraph

Claims 53-60 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner objects to the use of the term "stabilized form." The Examiner contends that only one stabilized form, phosphotriesters, is mentioned in the specification.

This term must be analyzed, not in a vacuum, but rather in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971). Applicant submits that the term "stabilized form" would have been definite to one of ordinary skill in the art. Firstly, the meaning of the term is definite from its ordinary usage. The term "stable," in the ordinary sense of the word, is defined as a substance which is "not easily decomposed or otherwise modified chemically." (Webster's II New Riverside University Dictionary (1988)). Therefore, a "stabilized form" of oligonucleotide is one which would not be easily decomposed or otherwise modified chemically.

Secondly, the term would be clearly defined to one of ordinary skill based on its usage in the specification. For example, on page 4, lines 28-31, it is stated that the "oligonucleotide . . . can be transformed to a more stable form, such as a phosphotriester form, to inhibit degradation . . . ." This statement was made in a discussion of one embodiment whereby the invention is used to inhibit the infection of a host organism by a foreign organism. Thus, to one of ordinary skill in the art, a stabilized form would be understood to be one which resists degradation by both the host and the foreign organism.

The term is also definite when viewed in light of the functionality of the oligonucleotide analogs to which it refers. For example, Miller et al. (*Nucleic Acids: The Vectors of Life* 521-535 (1983)) discussed the use of analogs to serve as selective inhibitors of cellular nucleic acid function. In referring to deoxyribonucleotide alkyl phosphotriesters and deoxyribooligonucleoside methylphosphonates, they emphasized the analogs' unique physical and biological properties including (1) their ability to form stable hydrogen-bonded hybrid complexes; (2) their resistance to hydrolysis by nucleases; and (3) their

ability to be taken up intact by mammalian and certain bacterial cells (page 521). (In citing post-filing date publications, the Applicant respectively points out that reference may be made to such publications to construe claim language and, in particular, to prove the definiteness of claim terminology. In re Glass, 181 U.S.P.Q. 31, 36, n.6 (C.C.P.A. 1974)). Jayaraman et al. (*Proc.Nat'l.Acad.Sci.*, 78(3) 1537-1541 (1981)) - (Exhibit F) also emphasized that it is these unique properties which allow for the analogs' utilization in inhibiting protein synthesis. Although not specifically using the term "stabilized form," it is clear that it is the analogs' resistance to degradation, their "stability," which makes their use so attractive in this field of art. Thus, one skilled in the art, knowing the purpose for utilizing the oligonucleotide analogs, would be possessed of a reasonable degree of certainty as to the exact subject matter encompassed within the claims. In re Moore, supra.

Section 103

The Examiner has rejected claims 53-61 under 35 U.S.C. § 103 as being unpatentable over Itakura et al. in view of either Paterson et al. or Hastie et al. in further view of either Summerton or Miller et al.

In an Interview with the Examiner on June 9, 1992, the Applicant's representative and the Examiner discussed the prior history of the application and its predecessors during which the Applicant had come to understand that rejection over the cited art had been successfully overcome. A copy of the Interview Summary is attached as Exhibit G. In that Interview the Examiner requested that copies of the relevant documents from the parent applications be resubmitted in this regard to overcome the present rejection. The following documents from the file history of Ser. No. 314,124, from which priority is claimed, are submitted herewith for the Examiner's consideration:

Exhibit H - Office Action of May 8, 1985: specific attention is drawn to pages 4-6;

Exhibit I - Examiner Interview Summary Sheet of October 18, 1985: specifically page 2 in which the Examiner indicated that, pending the limitation of the claims, he was favorably impressed regarding the arguments made in connection with all of the 103 rejections;

Exhibit J - Office Action of November 27, 1985: specifically page 3 where the Examiner indicated that limitation of the claims to the use of oligodeoxyribonucleotides as proposed by Applicants would overcome the rejection; and

Exhibit K - Amendment of April 1, 1986: specifically pages 1-2, where in broad claim 54 the "more stable form" of the oligodeoxyribonucleotide is not limited to any particular form.

It is respectfully submitted that since identical rejections were successfully addressed in the parent application, submission of the above identified documents is sufficient to overcome the present section 103 rejection.

Section 102(e)

Claims 53-61 have also been rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Ts'o et al (the '863 patent).

The above rejections were also made during the prosecution of the parent application. As discussed in the June 6, 1992 Interview, the Applicant is filing copies from the parent file history to overcome the present rejection. The Applicant is submitting the following documents for the Examiner's review:

Exhibit L - Advisory Action of March 22, 1989: specifically page 2, wherein the Examiner withdrew the rejections based upon the Ts'o reference in view of the Rule 131 Declaration

filed on March 3, 1989;

Exhibit M - March 3, 1989 Response;

Exhibit N - Rule 131 Declaration, signed by the Inventor;

Exhibit O - seven (7) documents submitted in support of the declaration which demonstrate prior conception and reduction to practice of the presently claimed invention.

It is respectively submitted that, in light of the similar arguments made in overcoming an identical rejection in the parent application, the present rejection should be withdrawn.

In light of the remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

Respectfully submitted,

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